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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/576,149

01/23/2007

David N. Watkins

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EXAMINER

HUFF, SHEELA JITENDRA

ART UNIT

PAPER NUMBER

1643

MAIL DATE

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/576,149	Applicant(s) WATKINS ET AL.	
	Examiner Sheela J. Huff	Art Unit 1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 March 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-5,7-17 and 19-60 is/are pending in the application.
- 4a) Of the above claim(s) 24-60 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5,7-17 and 19-23 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|----------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>3/3/09</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Response to Amendment

The amendment filed on 3/2/09 has been considered. Applicant's arguments are deemed to be persuasive-in-part.

Claims 1-5, 7-17 and 19-60 are pending.

Claims 24-60 are withdrawn from consideration as being drawn to a non-elected invention.

Claims 1-5, 7-17 and 19-23 are currently under consideration.

The objection to the claims is withdrawn in view of applicant's amendment.

The rejection under 35 U.S.C. 112, second paragraph, is withdrawn in view of applicant's amendment.

The rejection of claims 1-10, 13-20 and 23 under 35 U.S.C. 102(b) as being anticipated by WO 02/080952 is withdrawn in view of applicant's amendment/arguments.

The rejection of claims 1-6, 13-18 and 23 under 35 U.S.C. 102(e) as being anticipated by WO 03/088970 (filed 4/22/02) is withdrawn in view of applicant's amendments/arguments.

Information Disclosure Statement

The IDS filed 3/3/09 has been considered and an initialed copy of the PTO-1449 is enclosed.

Response to Arguments

Priority

Applicant argues that the provisional document is the same as that used in the 102(b) rejection. As stated in the previous action, the limitations of claims 10-11 and 20-21 are not mentioned in the provisional application and the provisional application is directed to inhibitors. The provisional application does not specifically mention agonists or antagonists and these terms are broader than the term "inhibitor". Furthermore, as amended the claims now recite cyclopamine, KAAD-cyclopamine, jervine, SANT-1, SANT-2, SANT-3 and SANT-4 and these compounds are not mentioned in the provisional application. Therefore, the priority date of the instant set of claims that are currently under consideration remains 10/20/04.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-5, 7, 13-17 and 19 remain rejected under 35 U.S.C. 102(b) as being anticipated by Watkins et al Nature vol. 422 p. 313 (3/20/03) as evidenced by Zhang et al Bioorganic and Medicinal Chemistry Letters vol. 18 p. 1359 (2008). The reasons for this rejection are of record in the paper mailed 10/31/08.

Applicant argues that in view of priority to 10/20/03 the document is only available as prior art under 35 USC 102(a) and submits a Katz declaration to overcome the 102(a) rejection. As stated above, the claims are not given the priority date of 10/20/03 and therefore the rejection remains under 102(b) and a Katz declaration cannot overcome a 102(b) rejection.

Claims 1-5, 7-9, 13-17, 19-20 and 23 remain rejected under 35 U.S.C. 102(e) as being anticipated by Dudek et al US 2004/0060568 (filed 10/13/00). This rejection is rewritten in view of applicant's amendments.

This reference discloses methods and reagents for the inhibition of undesired growth states that occur in cells with an active hedgehog signaling pathway. These

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cells overexpress the Gli gene ([0023]). The hedgehog antagonists are small molecules, such as cyclopamine and jervine ([0026], [0266] and [0168] and [0266]). The cancer to be treated includes small cell lung cancer ([0112]). This reference also discloses antibodies and antisense as hedgehog antagonists (489) and (502). Administration can be oral ([0609]). The invention in the reference is based on the discovery that signal transduction pathways regulated by hedgehog and/or gli can be inhibited by hedgehog antagonists (0066). The reference also discloses that unusually high levels of gli-1 levels are treated (and specifically discloses small cell carcinomas in the lung) with hedgehog antagonists as preferred embodiments ((0544) and shows data to support this (see Table 2). The reference also discloses conjunctive therapy using hedgehog antagonists (0621). Because the reference discloses the treatment of unusually high levels of gli, and specifically mentions small cell lung cancer, with hedgehog antagonists and since the reference discloses that cyclopamine and jervine are such antagonists, one skilled in the art would immediately envisage the treatment of small cell lung carcinoma with cyclopamine or jervine.

Response to applicant's arguments to the extent that they read on the above rejection.

Applicant argues that one skilled in the art would need to put forth inventive effort to practice the invention of Dudeck and specifically states that one would need to “established the link between the Hedgehog signaling, Gli1 overexpression and SCLC cell proliferation”. As stated above “The reference also discloses that unusually high levels of gli-1 levels are treated (and specifically discloses small cell carcinomas in the

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lung) with hedgehog antagonists as preferred embodiments ((0544) and shows data to support this (see Table 2)". Thus, the link has been established.

Applicant argues that those skilled in the art would need to test various hedgehog antagonists to determine which ones work. In view of the explicit disclosure of cyclopamine and jervine, one would immediately envisage the use of these.

Applicant argues that the reference provides little in the way of guidance and no working examples. The reference clearly provides data to show that Gli-1 is overexpressed in small cell lung carcinoma (table 2) and the reference shows in Example 3 that cyclopamine is a hedgehog antagonist. In fact, the reference shows this for several types of tissues such as breast, lung and prostate. And the reference goes even further to show that hedgehog antagonists (antibody) can be used to inhibit prostate tumor cells (example 6). Drawing an analogy between table 2 and Example 6 it is clear that prostate cancer which over expresses Gli-1 can be treated with hedgehog antagonists, one skilled in the art would immediately envisage the same for small cell lung carcinoma.

Claims 1-5, 8-17 and 20-23 are rejected under 35 U.S.C. 102(e) as being anticipated by Ling et al US 2005/0054568 (8/23/03). This rejection is re-written in view of applicant's amendments.

This reference discloses methods and reagents for the inhibition of undesired growth states that occur in cells with an active hedgehog signaling pathway. These cells overexpress the Gli gene (0010]+ and [0087]). The hedgehog antagonists include

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antibodies (including hedgehog antibodies) and small molecules (that read on steroidal alkaloid and derivatives thereof and specifically mentions cyclopamine in Example 3 as a hedgehog antagonist) and hedgehog mutants (see entire reference). The antagonists can be used alone or in combination ([0016]). The cancer to be treated includes small cell lung cancer ([0019] and [0614]). Administration can be oral ([0630]). These therapeutics can be used in combination with other chemotherapeutics ([0649]). The invention in the reference is based on the discovery that signal transduction pathways regulated by hedgehog and/or gli can be inhibited by hedgehog antagonists (0074). The reference also discloses that unusually high levels of gli-1 levels are treated (and specifically discloses small cell carcinomas in the lung) with hedgehog antagonists and shows data to support this (see Table 2). Because the reference discloses the treatment of unusually high levels of gli, and specifically mentions small cell lung cancer, with hedgehog antagonists and since the reference discloses that cyclopamine is such an antagonist, one skilled in the art would immediately envisage the treatment of small cell lung carcinoma with cyclopamine.

Response to applicant's arguments to the extent that they read on the above rejection.

Applicant argues that one skilled in the art would need to put forth inventive effort to practice the invention of Ling and specifically states that one would need to "established the link between the Hedgehog signaling, Gli1 overexpression and SCLC cell proliferation". As stated above "The reference also discloses that unusually high levels of gli-1 levels are treated (and specifically discloses small cell carcinomas in the

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lung) with hedgehog antagonists and shows data to support this (see Table 2)". Thus, the link as been established.

Applicant argues that those skilled in the art would need to test various hedgehog antagonists to determine which ones work. In view of the explicit disclosure of cyclopamine and jervine, one would immediately envisage the use of these.

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Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir.

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1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-5, 7, 13-17, 19 and 23 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 43-75 of copending Application No. 11/338503. The reasons for this rejection are of record in the paper mailed 10/31/08.

The person who signed the terminal disclaimer is not recognized as an officer of the assignee, and he/she has not been established as being authorized to act on behalf of the assignee. See MPEP § 324.

Claims 1-5, 7, 13-17, 19 and 23 remain directed to an invention not patentably distinct from claims 43-75 of commonly assigned 11/338503. . The reasons for this rejection are of record in the paper mailed 10/31/08.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5, 7-9, 11-17, 19-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dudek et al US 2004/0060568 (filed 10/13/00) in view of Chen et al PNAS vol. 99 p. 14071 (10/29/2002).

Dudek et al has been discussed above.

The only difference between the instant invention and the reference is the use of KAAD-cyclopamine,, SANT-1, SANT-2, SANT-3 and SANT-4, and the combination use of an antagonist with an anti-Hh antibody.

Chen et al disclose that SANT-1 to SANT-4 have hedgehog pathway inhibitory activities similar to cyclopamine (see page 14074, second column, second full paragraph) and that KAAD-cyclopamine is a potent cyclopamine derivative that is more potent in inhibiting hedgehog activity (page 14072, bottom of first column).

Thus, in view of Chen et al and the disclosure that SANT-1 to SANT-4 are as effective as and that KAAD-cyclopamine is more effective than cyclopamine, it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to use SANT-1 to SANT-4 or KAAD-cyclopamine in place of cyclopamine to inhibit small cell lung carcinoma. The combination of the antagonist with the antibody is obvious because Dudek discloses that anti-hH antibodies are effective hedgehog antagonists, and "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

Claims 1-5, 8-17 and 20-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ling et al US 2005/0054568 (8/23/03) in view of Chen et al PNAS vol. 99 p. 14071 (10/29/2002).

Ling et al has been discussed above.

The only difference between the instant invention and the reference is the use of KAAD-cyclopamine, SANT-1, SANT-2, SANT-3 and SANT-4, and the combination use of an antagonist with an anti-Hh antibody.

Chen et al disclose that SANT-1 to SANT-4 have hedgehog pathway inhibitory activities similar to cyclopamine (see page 14074, second column, second full paragraph) and that KAAD-cyclopamine is a potent cyclopamine derivative that is more potent in inhibiting hedgehog activity (page 14072, bottom of first column).

Thus, in view of Chen et al and the disclosure that SANT-1 to SANT-4 are as effective as and that KAAD-cyclopamine is more effective than cyclopamine, it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to use SANT-1 to SANT-4 or KAAD-cyclopamine in place of cyclopamine to inhibit small cell lung carcinoma. The combination of the antagonist with the antibody is obvious because Ling discloses that anti-hH antibodies are effective hedgehog antagonists, and "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

Conclusion

Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on 3/3/09 prompted the new ground(s) of rejection presented in this Office action. In addition, applicant's amendment filed 3/2/09 also necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS**

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MADE FINAL. See MPEP § 609.04(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheela J. Huff whose telephone number is 571-272-0834. The examiner can normally be reached on Monday-Thursday 6am to 2pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Sheela J Huff/
Primary Examiner
Art Unit 1643

sjh